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Roles of Ions in Formulation used for Collaborative Treatment of Disease

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ABSTRACT

Cancer is one of the problems of severe threats to human life and health. The aim of the present study was to examine the effects of calcium channel protein on cancer cells. Calcium is a versatile element that participates in cell signaling for a wide range of cell processes such as death, cell cycle, division, migration, invasion, metabolism, differentiation, autophagy, transcription, and others. Calcium channels may be generally categorized into two major classes: Voltage-gated calcium channels (VGCCs) and ligand-gated calcium channels (LGCCs). VGCCs may be classified into five subtypes: L type, N-Type, P-type, T-type and R-type. The immune system is specialized in the process of cancer cell recognition and elimination, and is regulated by different ion channels. The success of treatment depends upon the type of cancer, locality of tumor, and its stage of progression. Surgery, radiation-based surgical knives, chemotherapy, and radiotherapy are some of the traditional and most widely used treatment options. Some of the modern modalities include hormone-based therapy, anti-angiogenic modalities, stem cell therapies, and dendritic cell-based immunotherapy.

***KEYWORDS:** Ca^{2+} channels, Ion channels, voltage-gated ions, cancer therapy, tumors*

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INTRODUCTION

Calcium channels may be generally categorized into two major classes: Voltage-gated calcium channels (VGCCs) and ligand-gated calcium channels (LGCCs). VGCCs may be classified into five subtypes: L-type, N-Type, P-type, T-type and R-type. These ion channels have been implicated in the progression of numerous cancers. Ion channels are well recognized as important therapeutic targets for treating a number of different pathophysiologies. Cancer is one of the problems of severe threats to human life and health. Metal ions have a very important impact on life systems, and they play a necessary role that other chemical molecules cannot replace [1]. Excess, deficiency, and abnormal distribution of metal ions will seriously affect various physiological properties of cells. Finding new and innovative treatments for cancer is a major problem across the world[2]. Radiation therapy is one of the oldest modalities for cancer treatment and is currently prescribed to more than 50% of all patients. It is based on delivering high doses of ionizing radiation to well-localized tumor targets in the body. The goal is to kill all the tumor cells with acceptable toxic effects to the surrounding normal tissue, which is unavoidably exposed. Indeed, radiotherapy success is limited by the toxicity in the normal tissue. Metal ions signifcantly impact the biosystem and play an essential role in diverse physiological activities such as maintaining cell homeostasis, regulating metabolic pathways, substance synthesis, signal transmission, and energy conversion[3]. Metal ions have previously been used in imaging technology, such as the contrast agents based on Gd3+, which have dominated the MRI field for several decades [4]. However, the problems of traditional contrast agents limit their prospects for biological applications [5], such as insufficient time in vivo circulation of iodine-based and barium based agents [6] the short half-life period of radioactive 18F [7] and the high toxicity of gadolinium ions [8]. Ion channels are important drug targets because they play a crucial role in controlling a very wide spectrum of physiological processes [9] and because their dysfunction can lead to pathophysiology [10]. Given the strong historical precedent that exists for

discovering and commercializing successful drugs that modulate the activity of voltage-gated sodium, calcium, or potassium channels, or ligand-gated ion channels, new generations of therapeutic agents are expected to result from targeting this protein family.

Ion Channels in Cancer:

Ion channels comprise an important factor influencing the formation and development of tumors. Such malignant transformation leads to enhanced proliferation, abnormal differentiation, impaired apoptosis, and finally uncontrolled migration and Ion channels and anti-cancer invasion (Table 1). This is often associated with altered levels of ion channel expression as well as their activity in the mutated cancer cells[11]. The role of ion channels in pathogenesis of various diseases including cancer and its treatment has been extensively studied. The major types of ion channels implicated in carcinogenesis are presented below

Table 1: The role of distinct ion channels in cancer development and progression

Ion channels	Expression profile	Cancer type	References
Proliferation of cancer cells Shaker-like K+ channels (Kv1.1, Kv1.3, Kv1.5)	Gene and protein upregulation	Glioma, breast cancer, lung cancer, pancreas cancer, prostate cancer, lymphoma	12, 13
EAG K+ channels (EAG1, EAG2) Gene and protein upregulation	Gene and protein upregulation	Medulloblastoma, breast cancer, head and neck cancer, melanoma, gastrointestinal tract cancer	14-16
EAG-related K+ channels (HERG/Kv11.1)	Gene and protein upregulation	Melanoma, neuroblastoma, breast cancer	17
Ca2+-activated K+ channels (KCa3.1)0	Gene and protein upregulation	Glioma, breast cancer, lung cancer, pancreas cancer, prostate cancer, lymphoma	18-21
Cell migration and metastasis EAG K+ channels (EAG1/ Kv10.1)	Gene and protein upregulation	Migration of breast cancer cells	22
Ca2+-activated K+ channels	Gene and protein upregulation	Breast cancer → metastasis to brain Breast cancer → bone metastasis Migration of glioma cells, transformed renal epithelial cells and breast cancer cells	23-27
Tumor angiogenesis EAG K+ channels (EAG1	Gene and protein upregulation	Breast cancer and other solid tumors	

Ca2+ channels:

The intricate fluxion of Ca2+ ions between extracellular and intracellular stores shapes the movement of Ca2+, such as Ca2+ release, Ca2+ oscillations, and Ca2+ spikes, modulating numerous biological functions[28-29]. It is not surprising that the exchange of Ca2+ ions among different components of cells is interconnected and highly coordinated, and uncontrolled remolding of this well-connected network may lead to cancer cells metastasis to bone. Extracellular Ca2+ concentration is maintained at a high level (~1–2 mmol/L), which is 10–20,000 times that of the cytosolic Ca2+ concentration (~100 nmol/L). Endoplasmic reticulum (ER) stores intracellular Ca2+ ions, with a Ca2+ concentration around 100–400 µmol/L [30]. The regulation of this gradient is operated through a variety of mechanisms (Figure 1). Plasma membrane Ca2+ ATPases (PMCAs) and sarco(endo)plasmic reticular Ca2+ ATPases (SERCAs) are the main ATP-dependent channels that extrude Ca2+ ions from the cytosol to the extracellular space and ER, respectively. Inositol 1,4,5-trisphosphate receptors (IP3 Rs) initiate Ca2+ releasing from the ER [31]. After the depletion of the intracellular Ca2+ stores, store-operated Ca2+ entry (SOCE), a specific Ca2+ influx pathway, initiates Ca2+ influx through Orai1 Ca2+ channels after activation by the ER Ca2+ store sensor stromal interaction molecule 1 (STIM1 [32-33]. Extracellular Ca2+ ions enter the cytoplasm through substantial mechanisms and are the primary origin for intracellular Ca2+ signaling in cells. Examples include store-operated Ca2+ channels (SOCs), the transient receptor potential (TRP) superfamily of ion channels, voltage-gated Ca2+ channels (VGCCs) including L-, R-, N-, P/Q-, and T-type channels, and stretch-activated PIEZO channels [31,34-37].

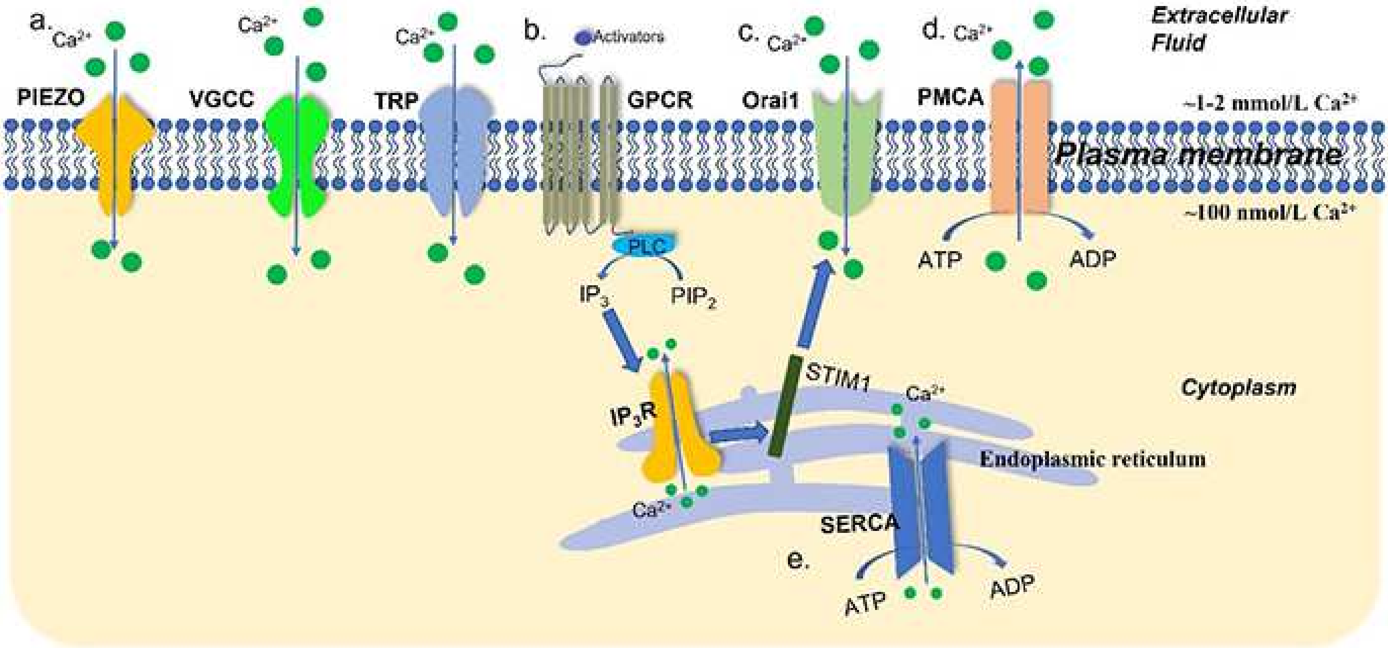

Figure 1. An overview of Ca2+ channels, transporters, and pumps in the plasma membrane and ER. Intracellular Ca2+ concentration is governed by a tightly mediated mechanism. (a) The TRP channels, VGCCs, and stretch-activated PIEZO channels are the Ca2+ channels and transporters in the plasma membrane; (b) after stimulation by activators, G-protein-coupled receptors (GPCRs) facilitate the dephosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol 1,4,5-trisphosphate (IP3) by phospholipase C (PLC). In turn, IP3 Rs initiate Ca2+ release from the ER; (c) STIM1 senses the depletion of the ER Ca2+ stores and activates Ca2+ influx via Orai1 Ca2+ channels; (d) PMCAs extrude Ca2+ ions from intracellular space to the extracellular space; (e) SERCAs transport Ca2+ from the cytoplasm into ER. ADP: adenosine diphosphate

Specific calcium channels or pumps as targets for cancer therapy

The overexpression of specific calcium channels and pumps in some cancer types and/or subtypes has led to the proposal that pharmacological modulators of some calcium channels or pumps may represent future cancer therapies. However, overexpression itself is not a sufficient criterion for a potential pharmacological target in cancer. Pharmacological modulation of the target must alter proliferation, migration and/or induce cancer cell death, analogous to the way anti-HER2 agents exploit the overexpression of the HER2 protein in some breast cancers to control disease progression [38]. The critical role of the calcium signal in many of the hallmarks of cancer [39] certainly gives the potential for an effective therapy. However, a lack of activity, defective membrane trafficking or a limited role of a specific calcium pump or channel in a pathway relevant to tumor progression are just some of the examples where over-expression per se will be insufficient for a calcium pump or channel to be a therapeutic target in a particular cancer type. Another consideration is the likely effects of global pharmacological modulation of the target. Although many cancer therapies work on targets with critical roles in normal cells, as exemplified by some of the major side effects of some anticancer agents (e.g. immunosuppression), this is an important consideration. Tools for target selection and/or prioritization could include consideration of the known toxicity of pharmacological modulators to the target, or where such agents are not currently available, the viability and/or phenotype of knockout animals. It should be noted that despite the diverse expression of some ion channels and ion pumps they still represent targets highly amenable to drug development. Indeed, ion channels have been reported to represent 19% of human protein drug targets and are the targets of existing therapies including L-type Ca^{2+} channel blockers for the control of hypertension [40].

A number of reviews have highlighted the potential of calcium permeable ion channels and calcium pumps as therapeutic targets [41,42]. An example where this approach has recently started to extend towards human clinical trials is for the targeting of the highly Ca^{2+}-selective ion channel TRPV6 [43]. Increased levels of TRPV6 have been reported in a variety of malignant cancers [44] including estrogen receptor negative breast cancers where TRPV6 overexpression may be driven by increases in TRPV6 copy number [45]. Silencing and overexpression studies have identified a critical role for TRPV6 in the proliferation of some cancer cell lines using in vitro and in vivo models [46,47]. TRPV6 inhibitors have now undergone human phase 1 clinical trials in patients with advanced tumors of epithelia origin including those of the ovary, colon, pancreas, breast and prostate [43]. Fig. 1 presents a conceptual overview of how an overexpressed ion channel could be

pharmacologically targeted for cancer therapy. The first approach is valid for ion channels that contribute to the proliferation and/or invasive pathways in cancer cells through effects on cytosolic Ca^{2+} signaling. For these targets pharmacological inhibition may attenuate these pathways to reduce proliferation and/or invasion. Example of this approach include the aforementioned TRPV6 as well as inhibitors of store operated calcium entry (SOCE) which target the remodeling of Orai1-mediated Ca^{2+} influx which appears to be a feature of some cancer types [48,49,50]. TRPV4 is another example, since TRPV4 silencing has recently been shown to reduce the invasiveness of breast cancer cells [51]. In the specific context of TRPV4, it is interesting to note the successful completion of a phase 2 clinical trial of the TRPV4 inhibitor GSK2798745 in patients with congestive heart failure [52], highlighting the potential for the repurposing of this compound and/or similar agents for the treatment of some cancers. Indeed, there is a variety of opportunities for the repurposing of agents targeting calcium permeable ion channels for cancer, such as T-type Ca^{2+} channel blockers such as mibefradil (previously used for cardiovascular disease) which is being assessed in clinical trials for glioblastoma multiforme [53], the most common and aggressive form of brain cancer. The focus of drug development programs for SOCE inhibitors (developed by companies such as CalciMedica and Rhizen Pharmaceuticals) for an array of conditions including autoimmune disorders [54] also represent opportunities for drug repurposing.

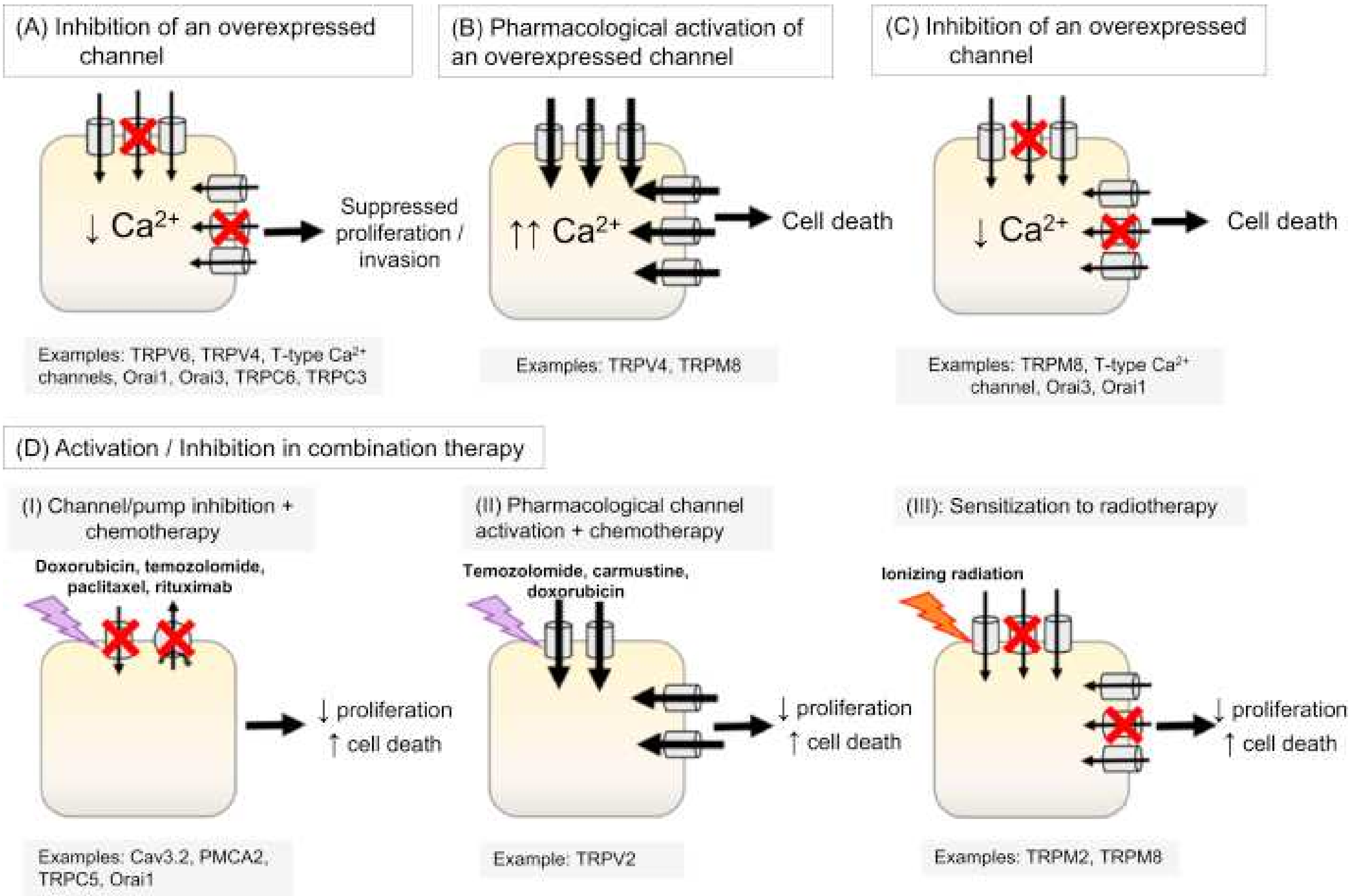

Fig. 1. Strategies to target Ca^{2+} signaling for cancer therapy. The overexpression of Ca^{2+} channels in cancer cells may be targeted by: (A) inhibition to suppress pro-proliferative or pro-migratory Ca^{2+} signals, examples of such channels include TRPV6 [47], T-type voltage-gated Ca^{2+} channels, i.e. Cav3.2 [55], Orai1 [50], Orai3 [56], TRPC6 [57] and TRPC3 [58]; (B) activation to promote Ca^{2+} overload and activating cell death (eg: apoptosis and oncosis), examples are TRPV4 [59] and TRPM8 [60]; or (C) inhibition to suppress pro-survival Ca^{2+} signals to induce cell death, examples include TRPM8 [60], T-type Ca^{2+} channels [61], Orai1 [62] and Orai3 [63]. Alternatively, Ca^{2+} signaling can also be strategically targeted in combination with anti-cancer drugs to promote killing of cancer cells (D). Proposed mechanisms include (I) inhibition of a Ca^{2+} channel such as Cav3.2 [64], TRPC5 [65] and Orai1 [66] or a plasmalemmal Ca^{2+} efflux pump such as PMCA2 [67]; (II) activation of a Ca^{2+} channel, eg: TRPV2 [68] to promote the cytotoxic effect of chemotherapy drugs such as temozolomide, doxorubicin and carmustine; or (III) inhibition of specific Ca^{2+} influx channels such as TRPM2 [69] and TRPM8 [70] in combination with radiotherapy to promote tumor-suppressing and/or cytotoxic effects.

Activation of Ca^{2+} permeable ion channels with pronounced overexpression represents another approach to promote cancer cell death, and this potential has now been demonstrated in a variety of

models including TRPV4 in breast cancer cells [59] and TRPM8 in prostate cancer cells [60]. However it should be noted as reflected also in fig: 2, that there may also be examples where inhibition of a plasmalemmal Ca^{2+} permeable ion channel may also induce cancer cell death. In these examples rather than direct "Ca^{2+} overload" inducing necrotic or apoptotic cell death, the attenuation of a Ca^{2+} influx pathway may induce cancer death through other pathways. Examples includes the ability of T-type Ca^{2+} channel inhibition to produce apoptosis in p53-competent HCT116 colon cancer cells through activation of p38-MAPK [61]. Another area of study has been the identification of calcium transporters, pumps and channels of intracellular organelles that when silenced can also attenuate pathways important in tumor progression. These examples extend to the recently identified components of mitochondrial Ca^{2+} transport and the less studied Ca^{2+} pumps of the Golgi apparatus – secretory pathway Ca^{2+} ATPases (SPCAs). Reduced expression of MCU in MDA-MB-231 breast cancer cells suppresses their migration in vitro and metastasis in vivo [71], and reduced expression of SPCA2 attenuates the proliferation of MCF-7 cells in vitro and tumor growth in vivo [72].

The discussion above has mostly focused on targeting specific calcium channels, pumps or exchangers through exploitation of their overexpression and/or critical role in a proliferation or invasive pathways. However, there may be circumstances where mutations in a Ca^{2+} regulating protein may be a feature of cancer cells. In some cases these events may be rare and confined to only a very few individual cancers, such as appears to be the case for gain of function mutations in Orai1 identified from the cBioPortal database [73]. Although further work on other calcium channels, pumps and exchangers is required, there is an example which does point to the potential significance of a mutation of a calcium pump in a cancer which leads to a significant clinical impact. Somatic mutations in the PMCA3 Ca^{2+} efflux pump in some aldosterone-producing adenomas reduces the activity of the PMCA3 pump and remodels Ca^{2+} signaling which appears to promote aldosterone production and the associated severe arterial hypertension in patients with these adenomas [74,75]. Whether the future will see highly selective agents targeting specific mutations of a calcium channel, pump or channel in a specific cancer type is still unclear, however such agents are theoretically possible given the successful development of CFTR ion channel mutation specific drugs for cystic fibrosis therapy [76].

Voltage-gated ion channels, cancer development, and metastasis

VGICs, in general, significantly contribute to a variety of mechanisms involved in cell survival and are crucial for maintaining normal tissue homeostasis, such as cell proliferation (77) cell migration (78), gene expression (79), vesicular patterning (80), apoptosis (81), and more.

All these mechanisms are critically important in maintaining and promoting cell activities but are also part of cancer cells proliferation. Increasing evidence supports ion channels in cancer cells *in vitro* and *in vivo*, revealing how they contribute to different aspects and stages of the cancer process.

According to their expression levels, several VGICs have been found to play essential roles during the cell cycle. Thus, aberrant ion channels' expression or malfunction can impair these processes, driving the transformation of normal cells into malignant ones that exhibit uncontrolled multiplication and spreading.

The following are a couple of examples:

Potassium channels: With 77 genes coding and many splice variants, the potassium channels are the largest, most diverse group of ion channels in the human genome. Voltage-gated potassium (Kv) channels play a pivotal role in the progression of various cancer types, including blood cancers such as leukaemia and lymphoma. Several studies have demonstrated an altered expression of the potassium channels subunits in cancer compared to normal tissues. However, the changes depend on the type and the stage of the disease.

In breast cancer, a significantly up-regulated expression of Kv1.3 channel mRNA is already observed in the first stage of the disease (82). Similarly, the human voltage-gated potassium channel ether *à go-go* 1 (EAG1, Ky 10.1) is overexpressed in most types of tumors, including leukaemia (83).

In the case of prostate cancer, instead, there is a significant inverse correlation between the expression of the Kv1.3 channels in the epithelium of human prostate tissue and the grade of the tumor (84).

Sodium channels: in a study by Fraser shows that, two rat prostate cancer cell lines with different metastatic abilities such as MAT-LyLu (strongly metastatic cell line expressing functional sodium channels) and AT-2 (weakly metastatic cell line with no functional sodium channels), were used in a comparative approach. The results plainly show that only the MAT-LyLu cells with functional VGSC

expression have enhanced prostate cancer cells' cellular motility (hence metastatic process) (85).

Another example is the expression of the sodium Nav1.5 ion channel in breast cancer. A study by Nelson shows that the Nav1.5 α subunit regulates breast tumor growth and potentiates migration and invasion, supporting the notion that compounds targeting Nav1.5 may help reduce metastasis (86).

A similar example is a study by Fraser showing that Nav1.5 expression is significantly up-regulated in metastatic human breast cancer cells and tissues compared with matched normal breast tissue and that Nav1.5 activity potentiates cellular directional motility, endocytosis, and invasion (87).

Other isoforms of Nav sodium channels such as Nav1.6 and Nav1.7 are involved in cervical cancer, breast, prostate, and non-small cell lung cancers.

Calcium channels: Calcium ion channels also have confirmed roles in cellular functions, including mitogenesis, proliferation, differentiation, apoptosis, and metastasis. For example, the expression of several calcium channels of the TRP superfamily is elevated in different common carcinomas, such as the TRPC1 in breast cancer, TRPC3 in some breast and ovarian cancer, TRPC6 in breast, liver, stomach, and glia cancers, and TRPM7 in breast, pancreas, ovarian and gastric cancers, to mention some.

The high voltage-activated Cav1.2 channel is overexpressed in most cancer types, including colorectal, gastric, leukaemia, brain, uterus, breast, pancreatic, sarcoma, skin, and prostate. Similarly, the Cav1.3 is highly expressed in most types of cancer, including breast and prostate cancer, brain cancer, colorectal, gastric, bladder, lung, oesophageal, and uterine tumors (88,89). Also, in breast cancer, a total of 5 VGCC family members (CACNA1A, CACNA1B, CACNA1E, CACNA1G, and CACNA1I) show a reduced expression.

Tumor biology

Cell division, when grows independent of growth factors, forms tumors, which involve a series of steps. In the very first stage, a large mass of cells known as hyperplasia is formed because of uncontrolled cell division. This is followed by dysplasia in which cell growth is accompanied with abnormalities. Additional changes occur in the next stage when these atypical cells start to spread over a limited area of the tissue, losing their original function. This phase is coined as anaplasia. At this stage, the tumor is not invasive and is considered as benign. In the advanced stage, the tumor cells acquire the ability to metastasize. They begin to invade the surrounding tissues as well as those located away via bloodstream. This stage is considered to be malignant and is very hard to treat. However, not all tumors progress to this level, if identified earlier [14]. Though tumor cells are able to proliferate independent of growth factors, they still require nutrients and oxygen for their growth. All normal tissues are sufficiently supplied with capillaries for the supply of nutrients and oxygen to every cell. Similarly, tumors, as growth progresses, form new blood vessels in a process called as angiogenesis so that nutrients reach the cells located at the center of the tumor mass which do have access to normal blood vessels [15].

The types of tumor

1. On the basis of the type of cell initially altered

Tumors are named depending upon the type of cell from which they originate. These include:

- Carcinomas, which result from altered epithelial cells. They constitute the highest ratio in all types of cancer.
- Sarcomas denote the cancer abnormalities in the bone, muscle, fats, and connective tissue.
- Leukemia, which originate from cancerous white blood cells.
- Lymphoma, which is a malignancy of the lymphatic system or cells which are derived from the bone marrow (BM).
- Myelomas depict the cancers of those particular white blood cells that synthesize antibodies [14].

2. Classification by grade

This is the abnormality in cells with respect to their surrounding normal tissues. Increase in abnormality increases the grade, from 1 to 4. Well-differentiated cells closely resemble normal cells and belong to low-grade tumors. Improperly differentiated cells are highly abnormal with respect to the surrounding tissues [16]. These are high-grade tumors.

Grade 1 : This includes well-differentiated cells having slight abnormality.

Grade 2 : These cells are moderately differentiated and a bit more abnormal.

Grade 3 : The cells are improperly differentiated and very abnormal in context of having mutated chromosomes and produce some harmful chemicals which affect nearby cells and may enter in the blood.

Grade 4 : Cells are immature, primitive, and undifferentiated

3. Causes of cancer

Origin and advancement of cancer depend on many factors inside the cell (mutations, immune conditions, and hormones) as well as external factors from the environment (smoking, chemicals, infectious organism, and radiations). These entire elements act

together to cause abnormal cell behavior and uncontrolled proliferation. The resultant unusual cell mass in the body grows and affects normal tissues in their surroundings, and sometimes it also spreads to the other localities in the body (metastasis) [17] (Figure 1). According to the most accepted model for cancer causation, mutations in tumor suppressor and oncogenes is the major factor leading to the cancer development. Another model suggests that some mutation in a master gene that control the division of cells can also shepherd normal cells toward abnormal chromosomal replication, which can result in duplication or deletion of the entire sections of chromosomes [18]. This change in genetic content in the cells produces abnormal amount of a specific protein irrespective of the actual need. If any chromosomal aberration affects a protein that plays a crucial role in cell cycle, quantitatively or qualitatively, it may result in cancer. There is also a strong indication that the unnecessary addition (hypermethylation) or deletion (hypomethylation) of methyl groups to genes involved in the regulation of cell cycle, DNA repair, and apoptosis is also associated with some cancers. It is necessary to commemorate that cancers can take months to years for accretion of DNA mutations enough for the resultant cancer mass to be detectable. Thus, there can be several mechanisms which lead to the development of cancer. This further obscures the difficult task of defining the actual cause of cancer [19].

➢ **Mutations in the p53 tumor suppressor gene**

Considering biochemical pathways the most important component central to human carcinogenesis is the P53 gene whose normal function is associated with gene transcription, DNA synthesis, apoptosis, and DNA repair [20]. Alterations and mutations in p53 elicit the development of primary tumors. The biochemical processes related to the normal function of p53 gene are performed by multiunit protein machines. The functions of these machines are altered by some viral oncoproteins, which bind with the p53 and perturb its interactions with other cellular protein components [21].

➢ **Linking tumor viruses to human cancer**

Development of human malignancies is strongly associated with viruses. In fact, 15% of the cancer are believed to be caused by oncogenic viruses which include human papillomaviruses (HPVs), Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpes virus (KSHV, also known as HHV-8), and hepatitis B and C virus (HBV and HCV) [22]. Another virus known as Merkel cell polyomavirus (MCPyV) has been recently described causing Merkel cell carcinoma, a rare but aggressive type of skin cancer [23]. The recent studies on these cancer-causing agents have been very helpful to understand the basic biology of cell and how disturbances in the cellular pathways lead to the initiation and maintenance of cancer.

RESULT AND DISCUSSION:

It is clearly evident in the literature, that Ca^{2+}-permeable channels, transporters and pumps play important roles in a wide range of cancer-related process.

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CONFLICT OF INTEREST:

All authors declared no conflict of interest for the work.

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